

**REMARKS**

This Amendment is responsive to the Office Action mailed October 30, 2008. With this submission, claims 1, 3, and 6 have been amended. Claims 1-13 are pending; claims 1-7 are under consideration; and claims 8-13 are withdrawn.

Support for the instant amendment can be found throughout the specification as filed, e.g., at page 3, last paragraph; page 9, line 14 through page 10, line 26; page 16, second paragraph, and original claim 2. No new matter has been added. Reconsideration and withdrawal of the rejections made in the above-referenced Office Action are respectfully requested in view of the following remarks.

Election/Restriction

Applicants thank the Examiner for reconsideration of the requirement for election/restriction set forth in the paper mailed June 11, 2008. Applicants note that the restriction requirement holding Group I (claims 1-7) to be under prosecution has been made final. Applicants further note that the Examiner has withdrawn claims 8-13 from consideration. The withdrawn claims remain pending, as they are subject to possible rejoinder.

Priority

Applicants also thank the Examiner for acknowledging receipt of all certified copies of the priority documents in this National Stage application.

### Information Disclosure Statement

Applicants thank the Examiner for acknowledgement of receipt of the Information Disclosure Statements filed August 15, 2005 and July 19, 2007. Applicants also thank the Examiner for considering all of the information listed in said Information Disclosure Statements, and for indicating such consideration with an electronic signature as well as an initialed notation at the bottom of the document.

### Specification

The Office Action objects to the specification for informalities. In particular, the Office Action objects to the embedded hyperlink and/or other form of browser-executable code on page 3, second paragraph. The Office Action also states that the brief description of Figure 10 on page 8 of the specification refers to “the amino acids sequence shown in SEQ ID NO:1,” although the sequence set forth in Figure 10 is not 550 amino acids long, whereas SEQ ID NO: 1 set forth in the sequence listing filed on December 27, 2004 indicates that SEQ ID NO: 1 is a 550 amino acid protein.

In response, Applicants submit that the instant amendment is fully responsive to the objections set forth in the Office Action mailed October 30, 2008. In addition, Applicants respectfully note that a replacement sequence listing was filed on April 14, 2006, and request the Examiner to consider the instant amendment in view of the sequence listing filed on April 14, 2006, and not in view of the sequence listing filed December 27, 2004. Accordingly, Applicants respectfully request that the objections to the specification be withdrawn.

Claim Objections

The Office Action objects to claim 3 for alleged failure to further limit claim 1.

In response, and without acquiescing to the propriety of the objection, Applicants submit that the instant amendment is responsive to the present objection, and respectfully request withdrawal of the same.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Office Action rejects claims 1-7 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the Office Action rejects claims 1 and 3-7, for allegedly omitting essential steps. The Office Action also rejects claim 3 for recitation of “the N-terminal fragment of Cochlin” in line 3. Finally, the Office Action rejects claim 6 for recitation of an antibody that recognizes an antigenic determinant contained in an amino acid sequence portion “corresponding to” amino acids at positions 36-127 of the amino acid sequence shown in SEQ ID NO: 1.

In response, and without acquiescing to the propriety of the rejections, Applicants submit that the instant amendment is responsive to the rejections set forth in the Office Action mailed October 30, 2008, and respectfully request withdrawal of the same.

Claim Rejections – 35 U.S.C. § 103(a)

The Office Action rejects claims 1-4 under 35 U.S.C. § 103(a), as allegedly unpatentable over Ikezono et al. (*Biochimica et Biophysica Acta* **1535**:258-65, 2001; hereinafter “IKEZONO”) in view of The Dictionary of Medicine, definition for the term “perilymph” (2000); Peter Collin Publishing, London; Retrieved October 21, 2008 from

<http://www.credoreference.com/entry/1051726/>), Magal et al. (U.S. Patent 6,274,554 B1; hereinafter "MAGAL"), Wall et al. (*Otolaryngol. Head Neck Surg.* **112**(1):145-53, 1995; hereinafter "WALL"), and Botstein et al. (U.S. Patent No. 6,913,919 B2; hereinafter "BOTSTEIN"). In particular, the Office Action asserts that IKEZONO discloses a method for detecting the protein product of the *Coch* gene in homogenized inner ear tissue samples. However, the Office concedes that IKEZONO fails to specifically teach the detection of Cochlin in a body fluid existing in the middle ear. For this missing feature, the Office relies on:

(1) the Dictionary of Medicine, which discloses that perilymph is a fluid known to exist in the labyrinth of the inner ear;

(2) MAGAL, which discloses that proteins can penetrate the membrane of the round window into the perilymph of the inner ear;

(3) WALL, which discloses that endogenous perilymph markers unique to the perilymph or cerebrospinal fluid, but absent in serum can be used to detect leakage of perilymph into the middle ear; and

(4) BOTSTEIN, which discloses that Cochlin is specifically expressed in the inner ear.

In response, Applicants submit that the claimed invention is not unpatentable over IKEZONO in view of the Dictionary of Medicine, MAGAL, WALL and/or BOTSTEIN. In particular, Applicants submit that WALL discloses the possibility of using of an endogenous substance, such as  $\beta$ 2-transferrin, which is unique to perilymph or cerebrospinal fluid, *but absent from serum*, as a way to detect perilymph fistula. However, neither WALL nor any of the other cited documents teach that Cochlin is unique to perilymph or cerebrospinal fluid, but absent from serum. Moreover, the  $\beta$ 2-transferrin disclosed in WALL is contained in cerebrospinal fluid and a small amount of  $\beta$ 2-transferrin is contained in serum. Therefore,  $\beta$ 2-transferrin would not

discriminate between perilymph fistulas and cerebrospinal fluid fistulas. In contrast, Cochlin is not contained in cerebrospinal fluid or in serum, as shown in Table 1 on page 37 of the instant specification. Therefore, by using Cochlin as an indicator, it is possible to clearly discriminate between perilymph fistulas and cerebrospinal fluid fistulas.

Applicants further submit that the other cited documents do not make up for the deficiencies of IKEZONO, the Dictionary of Medicine, and/or WALL. In particular, Applicants submit that BOTSTEIN teaches that Cochlin is expressed in the inner ear, i.e., the cochlea – not the perilymph. In other words, BOTSTEIN does not teach that Cochlin's expression is unique to perilymph, but absent from serum. Consequently, and contrary to the Office's assertion, one of ordinary skill in the art would *not* reasonably expect Cochlin to be expressed in perilymph and not expressed in serum.

The Office also takes the position that while IKEZONO did not separately analyze the perilymph component for the presence of Cochlin, one of ordinary skill in the art would reasonably expect Cochlin to be found in perilymph because MAGAL discloses that proteins can penetrate into the perilymph via the membrane of the round window. This rationale appears to be flawed for at least two reasons. First, when considered in context, MAGAL appears to disclose that proteins are capable of penetrating the membrane of the round window into the perilymph of the inner ear *when a protein is accompanied by a suitable vehicle and/or agent*. For example, MAGAL discloses that artificial perilymph is a “particularly suitable vehicle for introducing neurturin into the inner ear by penetration through the round window membrane.” (MAGAL at column 20, lines 49-51.) MAGAL also discloses that “the formulation of the neurturin protein product with an agent, such as injectable microspheres or liposomes into the middle ear” may provide for “the slow or sustained release of the protein.” (MAGAL at column 20, lines 54-59.)

Second, it is not possible to argue that Cochlin expression is both unique to perilymph or cerebrospinal fluid, but absent from serum, AND that one of ordinary skill in the art would expect to find Cochlin in the perilymph as a result of leakage from surrounding tissue. The Office may simply not have it both ways.

Accordingly, Applicants submit that IKEZONO in view of the Dictionary of Medicine, MAGAL, WALL and/or BOTSTEIN, either alone or in combination, do not disclose or suggest the instant invention, and respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

The Office Action also rejects claims 4-7 under 35 U.S.C. § 103(a), as allegedly unpatentable over IKEZONO, in view of the Dictionary of Medicine, MAGAL, WALL and BOTSTEIN as applied to claim 1 above, and further in view of Robertson et al. (*Human Molecular Genetics* 10:2493-2500, 2001; hereinafter ROBERTSON), the Academic Press Dictionary of Science and Technology (definition for the term “polyclonal”; Oxford: Elsevier Science & Technology (1996); retrieved October 22, 2008 from <http://www.credoreference.com/entry/3144515/>) and Wolfe, S.L. (*Molecular and Cellular Biology*, 1993, pages 790-93; hereinafter WOLFE).

In response, Applicants submit that the claimed invention is not unpatentable over IKEZONO, in view of the Dictionary of Medicine, MAGAL, WALL and BOTSTEIN as applied to claim 1 above, and further in view ROBERTSON, the Academic Press Dictionary of Science and Technology and WOLFE. In particular, Applicants refer to the comments set forth above with respect to the IKEZONO, Dictionary of Medicine, MAGAL, WALL and BOTSTEIN documents. In addition, Applicants submit that none of the additionally cited documents in the rejection of claims 4-7 under 35 U.S.C. § 103(a) appears to compensate for the deficiencies

present in the rejection of claim 1 over IKEZONO, in view of The Dictionary of Medicine, MAGAL, WALL and BOTSTEIN.

For at least the foregoing reasons, Applicants submit that IKEZONO, in view of the Dictionary of Medicine, MAGAL, WALL and BOTSTEIN as applied to claim 1 above, and further in view of ROBERTSON, the Academic Press Dictionary of Science and Technology and WOLFE, either alone or in combination, do not disclose or suggest the instant invention, and respectfully request withdrawal of the rejections under 35 U.S.C. § 103.


**CONCLUSION**

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

No additional fee is believed due at this time. If, however, any additional fee is necessary to ensure consideration of the submitted materials, the Patent and Trademark Office is hereby authorized to charge the same to Deposit Account No. 19-0089.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully Submitted,  
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